American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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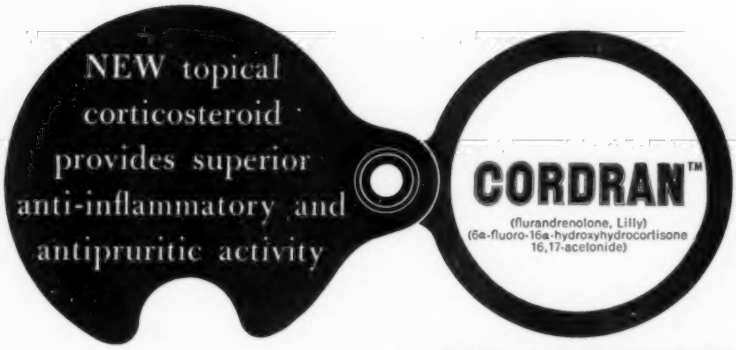
Since 1825 *October 1961*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Second Class Postage Paid at Philadelphia, Pa.



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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 133 OCTOBER 1961 No. 10

CONTENTS

E D I T O R I A L

NOW IS THE HOUR

THE death of John W. Dargavel brought an end to the career of one of pharmacy's most resolute warriors of all time. Fighting for the cause in which he believed was one of Dr. Dargavel's characteristics and one which kept him at the top of the N. A. R. D. for over two decades. The question remains, however, whether this will to do battle was invariably directed only against pharmacy's opponents.

The long-standing bitterness which could be sensed between the N. A. R. D. and the A. Ph. A. has surely not been conducive to progress for the profession. At times, it has seemed that those responsible for N. A. R. D. policy considered the interests of the "retail druggists" of the United States diametrically opposed to those of the profession at large. While this attitude may have been lacking in logic, none can question its acceptance by a sizable majority of the N. A. R. D. members and their endorsement of the leadership determining this policy.

At the last convention of the N. A. R. D., according to all reports, there was considerable uneasiness, to say the least, over some of the irresponsible attacks made against the A. Ph. A. largely because of its efforts to assist the defendants in the Northern California Antitrust Case. The spectacle of the N. A. R. D. giving support to those prosecuting pharmacists including N. A. R. D. members was apparently too much for even the tried and true in the association's hierarchy to stomach. The same could be said of the public denunciation of officers and representatives of the American Medical Association with which the profession of pharmacy tries to maintain cordial relations.

The source of all this friction was not, as alleged, the "evil" policy and program of the A. Ph. A. or the "machination of its scheming, ambitious" Secretary. The real difficulty lay in the diminishing purpose and program of the N. A. R. D. as contrasted with the en-

livened, energetic, and revitalized A. Ph. A. Keeping the N. A. R. D. going requires important causes that must be fought for—such issues, for example, as Fair Trade which over the years has mobilized retailers more than any other single cause. Regardless of which way the present legislative effort for Fair Trade goes, this *cause célèbre* has just about been exhausted. On top of this, retail pharmacists are beginning to have lurking doubts whether their key to survival really lies solely in efforts to protect the small businessman. Some even point to the independent grocer and others of a by-gone age in our distributive system. The more enlightened of pharmacy's retailers have already sensed that professional status is their only hope and their disaffection from the ranks of "retail druggists" operating a combined restaurant, hardware store, and five-and-ten is already in evidence. So, too, has there been increasing recognition that the A. Ph. A. is the real champion of the profession and its only hope of organized effort to protect such status.

While the N. A. R. D. continues to be of service to the owners of retail pharmacies, it should not and must not be permitted to obstruct the program of the A. Ph. A. for *all* pharmacists. The thing at stake here is of such paramount importance that the chance of this continuing or not should not be left to the change in the person or personality of its Secretary. It is a matter of simple human psychology that any Secretary is likely to find some grounds for criticizing another's actions. It is the old competitive spirit and self-justification at work. By the same token, none is so foul as the face and work of one's successor, as anyone who has retired must admit is true with few exceptions.

Only one solution to this, pharmacy's number one problem, remains. The N. A. R. D. should return home to the A. Ph. A. from which it never should have parted. Only as an affiliate of the A. Ph. A. can united, effective action be accomplished, as it is with the other A. Ph. A. affiliates, yet, its identity and relative autonomy could still be preserved. The next step would be the development of an integrated county, state, and national professional organization which is our most crying need. As long as we have two competing national organizations, this latter step can never be accomplished.

If those who have inherited power and influence within the N. A. R. D. would truly serve pharmacy, this is the time and the

hour. The needs of the profession are critical and nothing would add greater strength and impact in our efforts to meet them than integrated, united planning and action. Do those now in positions of leadership within the N. A. R. D. have the vision and courage to take the steps to bring the two organizations together? If they do, future generations of pharmacists will call their names blessed and pharmacy may yet achieve that position it justly deserves.

L. F. Tice

PURIFICATION OF SOME STEROIDS BY PHASE SOLUBILITY ANALYSIS [1]

By William H. Parsons,[2] Alfonso R. Gennaro,[3] and Arthur Osol [3]

THE determination of purity of adrenocortical steroids is a problem that received limited attention in the years preceding the early 1950's since only very small amounts of the compounds were available and because of the lack of suitable criteria of purity. Steroids are often difficult to crystallize; they may form solvates and are sometimes heat labile. Comparison of physical properties requires reference standards of such purity as to make their procurement difficult. Accordingly, the application of phase solubility analysis as a technique for purifying steroids and for determining their purity was undertaken.

Analyses based on freezing and melting curves have been used successfully, but melting point methods are usually inapplicable to steroids since some of them are heat labile and give decomposition ranges rather than equilibrium melting points (1).

Countercurrent distribution methods such as that described by Craig (2) have the disadvantage of requiring considerable experimentation to find a sufficiently selective solvent system. Chromatographic methods (3) share this disadvantage, and quantitative estimation of the components of mixtures is sometimes inadequate.

Considering the limitations of the preceding methods for determining the purity of steroids, the solubility criteria of purity first described by Northrop and Kunitz (4) suggested a useful method for the analysis of steroids. The solubility method of analysis is applicable to all species of molecules; knowledge of the nature of impurities present is not mandatory (3). It is based on the fundamental thermodynamic principles of heterogeneous equilibria.

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[1] This paper is abstracted, in part, from the thesis of W. H. Parsons, submitted to the Graduate School of the Philadelphia College of Pharmacy and Science in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1960.

[2] Present address: Department of Physics, Massachusetts College of Pharmacy.

[3] School of Chemistry, Philadelphia College of Pharmacy and Science.

Solubility analysis measures not only the amount of a single impurity in a system, but also the number of components present, as well as the solubility of the major component and of each of the impurities. In addition, if there is impurity present, a separation is effected so that, in the course of the analysis, very nearly pure material can be obtained from a sample that was initially relatively impure. Furthermore, all of the sample can be recovered; only simple equipment is required, and relatively little "working time" is necessary.

This type of analysis has been applied to nine steroids in this study as a research tool in the preparation of purified steroids and as a method for the determination of their purity.

The theoretical development of the solubility method of analysis has been thoroughly discussed by Northrop and Kunitz (4), Herriott (5), and Webb (6). It is based on the principle that a solution saturated with a pure component will be of constant composition regardless of the amount of the excess of the solid phase. If, however, the solid contains two or more components, the amount of material in solution will be a linear function of the total amount of solid added to the system until saturation with respect to both major and minor components is attained. The slope of a graph in which solute concentration is plotted against the total amount of solid per unit mass added to the system thus yields a measure of the purity of the solute. Also, the solubilities of the various components of a mixture can be calculated from the same graph, as will be explained in the experimental portion of this paper.

Characteristic of phase solubility analysis, a system in which solid phase is in equilibrium with solution not yet saturated with the other components is one in which the solid usually consists only of the "pure" major component. Based on this principle, quantities of the "pure" steroids sought in this study were obtained.

The solubility method of analysis fails to give a measure of the amount of impurity in a solute in only two theoretical cases: when the solute mixture consists of a solid solution, and when it consists of two or more components present in the unique ratio of their solubilities. Tarpley and Yudis (3) describe the types of phase diagrams obtained in these two cases.

A further limitation that might be encountered in this type of analysis is nonideality of solution, but this can be minimized or eliminated by working in dilute solution (*7*). A mixture of two or more crystalline polymorphic forms of a compound will, if equilibrium has been reached, give the phase diagram of a single compound. The rate at which equilibrium is reached may vary widely for the two forms. Previous crystallization from the solvent system to be used in the phase solubility analysis should assure that the crystalline form most stable under the conditions of the analysis would be in predominance (*3*).

Experimental

The solubility method involves the mixing of different masses of a solid sample with known masses of solvent until equilibrium is attained. The equilibration is generally carried out in sealed glass ampuls. The solid phase is then separated from the solution and the concentration of solute in the solution is determined. This solution concentration is plotted against the total amount of sample added per unit mass of solvent (system concentration). Choice of a suitable solvent or solvent system is of primary importance in the analysis. Best results are obtained when solubilities lie between 4 mg. per Gm. and 20 mg. per Gm. Solubility values much in excess of the upper limit require large amounts of sample, while those below the lower limit may involve high percentages of error since the precision of the analytical balance then becomes the limiting factor. For ease of measurement and evaporation, the boiling point of the solvent should not be below 50° and not greatly in excess of 100°C.

Precise data can usually be obtained with from six to eight solute-solvent systems in an experiment designed to consume minimum amounts of sample. Only a rough estimate of the solubility need be known beforehand. At least two ampuls should contain an amount of solid insufficient to attain saturation and the concentration of the solution in these ampuls should be as evenly spaced as possible between zero and saturation percentage. The slope of the phase solubility curve in this region should be unity, and the degree of conformity to this value provides a check on the precision of the experimental method and technique. The portion of the diagram which is most pertinent to this study is the region of system concentration above saturation. In this study, systems were set up in

which the concentration varied from just above saturation to approximately six times saturation concentration. This provided for the plotting of a sufficient number of points following the abrupt break in the solubility curve to define unequivocally the slope of the line—which is the measure of impurity present in the sample.

Procedure

The requisite amount of finely ground steroid, which had been previously crystallized from the solvent system to be used in the analysis and dried in a vacuum oven for eight hours at 40°C., was transferred to a U. S. P. Type 1 glass ampul of 20-ml. capacity. The ampul had been previously cleaned with steam, rinsed twice with purified water, and dried in a vacuum oven for eight hours at 40°C. It was cooled to room temperature in a desiccator and its mass [4] was determined to $\pm$ 0.01 mg. on a SEKO model 672 semimicro balance. Transfer of the steroids was accomplished using a small long-stemmed funnel, care being taken that no solid adhered to the neck of the ampul. The amount of solid added was determined to $\pm$ 0.01 mg. by the increase in mass of the filled ampul. The ampul and steroid were then placed in a dry ice-acetone bath for approximately ten minutes. Twenty ml. of previously purified redistilled solvent was added by means of a long 18-gauge hypodermic needle attached to a 20-ml. syringe. After chilling the systems in the bath for another five minutes, the ampuls were sealed. Any ampuls that showed leaks, after they had been placed in a dilute aqueous solution of methylene blue for two hours, were rejected. The remainder were dried in a vacuum oven at room temperature for eight hours and their masses were determined. System concentrations in terms of mg. of sample added per Gm. of solvent were calculated.

The systems were agitated by end-over-end rotation of the ampuls at 32 rpm in a water bath at 25 $\pm$ 0.02°C. for a period of five weeks, during which time equilibrium was reached. The positions of the ampuls on the rotor were reversed at two different times to change the direction of rotation in order to prevent clumping in the constricted part of the ampuls.

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[4] The term "weight" used in current chemical literature to denote measurements made using the analytical balance has the same connotation as the term "mass" used throughout this study.

The usual method of determining the amount of solid in solution is to determine the dry mass of the solute after evaporating the solvent from an appropriate aliquot of the solution. Accordingly, a 15-ml. aliquot was removed using a 20-ml. hypodermic syringe fitted with a long 18-gauge hypodermic needle. In the fitting at the end of the needle was placed a pledget of cotton to act as a filter. Immediately upon withdrawal of the aliquot, the needle and cotton filter were removed, and the aliquot was injected into a previously dried 50-ml. weighing bottle fitted with a standard-taper ground-glass top. The mass of the bottle and aliquot was then determined to $\pm$ 0.01 mg. (The mass of the bottle had been previously determined to $\pm$ 0.01 mg.) Each of the solutions was evaporated to approximately one-tenth of its original volume, using an electric hot plate over which had been placed a sheet of copper. Thereby, the temperature could be kept at approximately 45°C., even heating was assured, and spattering avoided. Evaporation to dryness was accomplished in a vacuum oven in which the open bottles and residues were placed for a period of eight hours at a pressure of 50 mm. of mercury and a temperature of 40°C. The bottles with the residues were then placed in a large desiccator containing silica gel as a desiccant, and allowed to cool to room temperature, after which the masses were determined to $\pm$ 0.01 mg. and the solution concentrations calculated in terms of mg. of solute per Gm. of solvent.

Curves relating the amount of solute per Gm. of solvent to the amount of solid added initially per Gm. of solvent were plotted. The amount of impurity was calculated from the slope of that portion of the curve immediately following the point at which an insoluble phase first appeared. For a pure material, this slope will be zero. For an impure substance containing one contaminant, the mass fraction of the contaminant is equal to the slope of the curve. The solubility of the major component is given by the Y-intercept of this portion of the curve, while the solubility of the minor component is given by the intercept of the constant solubility curve minus the Y-intercept corresponding to the solubility of the major component.

Systems containing several impurities may produce phase diagrams with several points of inflection, each corresponding to a component. For such systems, the total amount of impurity is given by the first slope, while the mass fraction of the individual impurities may be computed from the difference in slopes on either side of each point of inflection.

Results and Discussion

The following adrenocortical steroids[7] were analyzed and purified by the method of phase solubility analysis described in the preceding section: cortisone, cortisone acetate U. S. P., hydrocortisone U. S. P., hydrocortisone acetate U. S. P., hydrocortisone succinic acid, prednisolone U. S. P., prednisolone acetate U. S. P., prednisone U. S. P., and prednisone acetate.

Hydrocortisone succinic acid, obtained by converting the U. S. P. sodium salt to free acid, was selected for the study, in preference to the salt, because of the more nearly ideal behavior of the former in a phase solubility analysis.

Each compound was recrystallized at least once from the solvent or solvent system used in the solubility analysis to make certain that polymorphism, if existent, would be minimized. This was merely a precautionary measure. Tremer (8) maintains that prednisolone exists in no less than six polymorphic forms which would result in multiple points of inflection on the solubility curves. However, Hayes and [illegible] ([illegible]) indicate that various crystalline forms of the [illegible] if given sufficient time to attain equilibrium, [illegible] a single pure compound. Single points of inflection on the solubility diagrams [illegible] this.

Figure 1 is representative of the solubility curves obtained in which the slopes indicate that the steroids were purified until the [illegible] purity of approximately 99.5 per cent [illegible] would be [illegible] by a 0.5 per cent [illegible] of the slope of the curve. Usually, recrystallization from the solvent used in the analysis was sufficient to produce this degree of purity. When this was not the case, excess solids from the systems showing the greatest degree of [illegible] in solubility [illegible] recrystallized from the same solvent [illegible]. This latter procedure provided compounds sufficiently pure to serve as "reference standards" for the sample products. [illegible] solubility analysis [illegible] to increase [illegible] method for purity determination. [illegible] crystallization-purification [illegible]

[7] [illegible]

(3) state that ± 0.5 per cent is the limit of significance that can be placed on the technique.

The circles (O) in Figure I refer to solubility data obtained with once-recrystallized hydrocortisone, while squares (□) designate

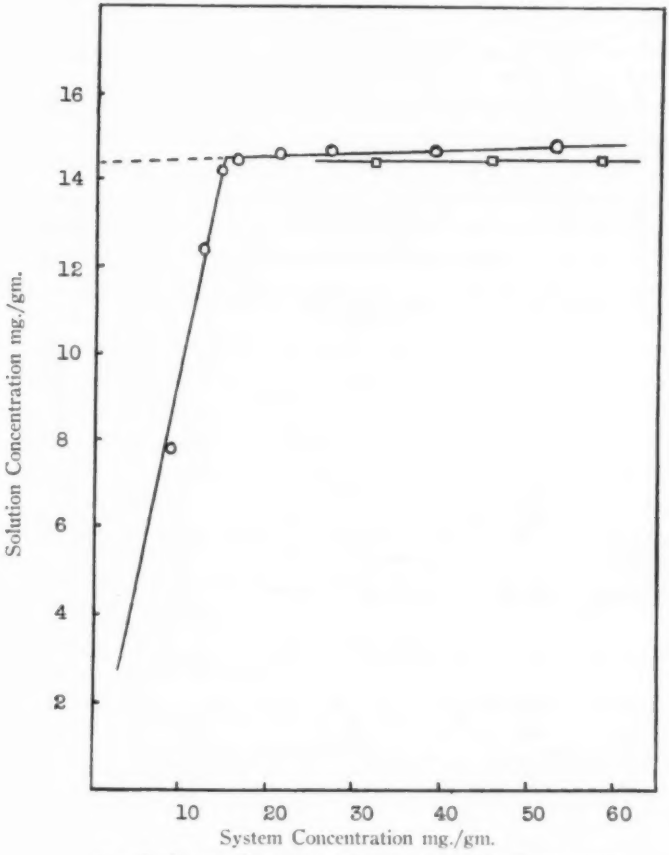

FIG. I. PHASE SOLUBILITY ANALYSIS OF HYDROCORTISONE

Solvent: Methanol

Solubility: 14.39 mg./gm. at 25 ± .02°C.

Slope: 0.67% corresponding to a purity of 99.3% after one methanol crystallization (O)

0.15% corresponding to a purity of 99.8% after two such crystallizations (□)

Results and Discussion

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Each compound was crystallized at least once from the solvent or solvent system used in the solubility analysis to make certain that polymorphism, if existent, would be minimized. This was merely a precautionary measure. Trenner (8) maintains that prednisolone exists in no less than six polymorphic forms which would result in multiple points of inflection on the solubility curves. However, Tarpley and Yudis (3) indicate that various crystalline forms of the same compound will, if given sufficient time to attain equilibrium, analyze as a single pure compound. Single points of inflection on the solubility diagrams demonstrate this.

Figure I is representative of the solubility curves plotted, in which the slopes indicate that the steroids were purified until the analysis showed a purity of approximately 99.5 per cent (which would be indicated by a 0.5 per cent inclination of the plateau of the curve). Usually one crystallization from the solvent used in the analysis was sufficient to produce this degree of purity. When this was not the case, excess solute from the systems showing the greatest degree of constancy of solubility was removed, dried, recrystallized from the same solvent, and reanalyzed. This latter procedure provided compounds sufficiently pure to serve as "reference standards" for any future analysis. Thus, solubility analysis was utilized both to increase sample purity and as an analytical method for purity determination. It was not deemed necessary to extend the crystallization-purification-analysis beyond 99.5 per cent purity since Mader (7) and others

[5] We acknowledge gratefully contribution of generous supplies of cortisone, cortisone acetate, hydrocortisone, hydrocortisone acetate, prednisolone, prednisolone acetate, prednisone, and prednisone acetate by Merck & Co., Inc., and of hydrocortisone sodium succinate by The Upjohn Co.

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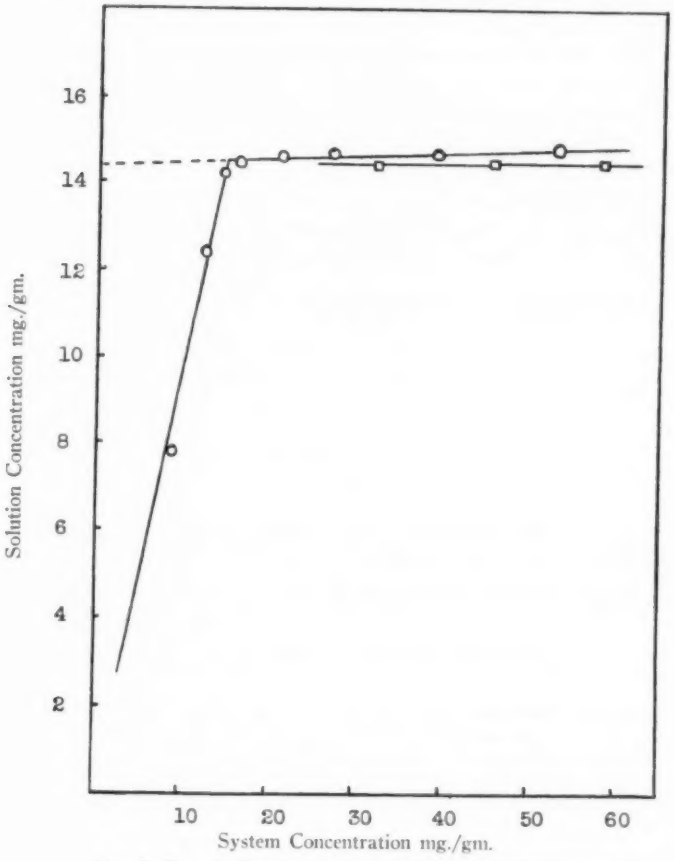

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solubility information obtained after removal, drying, recrystallizing from absolute methanol, and reanalysis of excess solute from those hydrocortisone systems in which the greatest degree of constancy of solubility was demonstrated. In each case in which a second analysis was required, the second equilibration period was three weeks in duration.

Table I lists the compounds analyzed, the solvent system used, the degree of purity after one crystallization, the purity after a second crystallization and analysis (when deemed necessary), and the extrapolated solubility in mg. of solute per Gm. of solvent system.

It was not a specific purpose of this study to determine the absolute value of the solubilities of the compounds analyzed but the agreement of the data herein reported with such data as are available in the literature is within experimental error. It is emphasized that

TABLE I

Compound	*Solvent System*	*Purity after one crystallization (per cent)*	*Purity after re-analysis*	*Extrapolated Solubility (mg. solute per Gm. solvent at 25°C.)*
Cortisone	80% Benzene-20% Chloroform	99.6	—	1.15
Hydrocortisone	Anhydrous Methanol *	99.3	99.8	14.39
Hydrocortisone Acetate	Anhydrous Methanol *	99.9	—	5.01
Cortisone Acetate	Anhydrous Methanol *	99.5	—	16.05
Hydrocortisone Succinic Acid	90% Benzene-10% Isopropyl Alcohol	97.9	99.3	9.89
Prednisone Acetate	95% Benzene-5% Methanol	99.1	99.7	27.01
Prednisolone Acetate	Anhydrous Methanol	99.7	—	10.19
Prednisolone	95% Benzene-5% Methanol	99.5	—	5.89
Prednisone	Anhydrous Methanol	99.4	99.7	11.21

* Indicates solvent systems used by Mader (7).

an object of this study was to obtain "pure" samples of steroids, utilizing constancy of solubility as a measure of purity. In a later paper, quantitative infrared data for estimation of these steroids, when present in binary mixtures prepared from the "pure" steroids, will be reported.

Summary

The technique of phase solubility analysis has proven to be a suitable method for:

1. Obtaining a series of steroids (cortisone, cortisone acetate, hydrocortisone, hydrocortisone acetate, prednisone, prednisone acetate, prednisolone, prednisolone acetate, and hydrocortisone succinic acid) of at least 99.5 per cent purity.

2. Determining the degree of purity of these steroids.

3. Determining accurately the solubility of the several steroids in the solvent systems employed, at the temperature specified.

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CURRENT CONTROL OF THE CHRONIC LEUKEMIAS WITH NITROGEN MUSTARDS

By John R. Sampey *

NITROGEN mustards have been among the most frequently employed agents in the management of the chronic leukemias since 1949 (38, 39). The chemical syntheses of scores of new derivatives of this class of alkylating agents have served to stimulate increased clinical trials in the control of malignant blood diseases. The present study was undertaken to determine which of the new N-mustards are proving most effective in current (since 1959) clinical trials in patients with chronic lymphocytic leukemia and chronic granulocytic leukemia.

Chronic Lymphocytic Leukemia

Chlorambucil. Chlorambucil,N,N-di(2-chloroethyl-p-aminophenyl)-butyric acid, also known as Leukeran, or CB 1348, is the agent of choice among N-mustard drugs in the current control of chronic lymphocytic leukemia, for it has been tested more extensively than the combined clinical trials with a dozen other N-mustards. Bethell and associates (4) described 41 satisfactory remissions in 47 patients treated with chlorambucil. In a cooperative study of the Cancer Chemotherapy National Service Center (7), 65 per cent of 40 patients with chronic lymphoid leukemia had good or excellent responses to CB 1348 which was better than that induced by myleran. Scott (41) reported that this butyric acid mustard has been the choice for the last three years and he tabulated 40 per cent remissions in 52 patients. Rundles *et al.* (37) in a cooperative study induced good or excellent responses in 15 of 23 patients, with two fair and six questionable responses; these results were superior to the three fair and nine questionable returns noted in 17 patients who received myleran. Miller *et al.* (30) secured six marked and six moderate objective remissions in 19 patients, which averaged 10.9 months, following chlorambucil therapy. In the first of two current studies (26), Libansky *et al.* induced 10 remissions in 14 patients and, in a second study (27), they

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described four remissions in four patients after the first treatment with leukeran, followed by eight responses in eight treatments of six patients; none of the remissions was complete, but one lasted 12 months. Grozea *et al.* (15) obtained a sense of well-being in 10 of 11 patients with CB 1348, and they added that 80 per cent showed a reduction in the sizes of lymph nodes and a normal leukogram. Anglesio (2) treated six patients and judged that four approached normal health for about six months ("very good" remissions), while one showed little or no improvement ("scarce" response). Desai (9) obtained good remissions in all five patients treated with chlorambucil, with the response lasting to 26 months. Silverberg and Lee (46) did not think the improvement after CB 1348 treatment was as good as that induced by TEM (triethylene melamine), but they used some combination therapy with TEM and X-rays, so that evaluation of the results is difficult. Grifoni *et al.* (14) reported good to excellent therapeutic results in a number of patients with a variety of lymphomas, including chronic lympocytic leukemia. In a panel discussion (19) on the comparison of the effects of CB 1348 versus radioactive phosphorus, Sprague concluded that there was little difference in the effectiveness of the two agents in 120 patients with chronic lymphocytic leukemia.

Dopan. Dopan, 5-bis(2′-chloroethyl)amino-uracil, also known as U-8344, or uracil mustard, has been tested on more than three score patients with chronic lymphocytic leukemia. In 1959, Shanbrom *et al.* (42) reported good response in 11 patients and, the next year (43), they recorded similar results in 17 more patients without giving the number of remissions in the chronic cases; in a third release (44), they listed 14 subjective and 14 objective improvements; they added that the drug was well tolerated with a minimum of nausea, pruritis, nervous irritability, and other side effects. Kennedy and Theologides (23a) described nine objective improvements in 15 patients, and they observed fewer side effects on oral administration of the drug; in 1961, these investigators (23b) induced 15 objective and 12 subjective responses in 19 patients, with four of the improvements lasting more than 12 months. Spurr and Hayes (47) described five subjective and objective improvements in seven patients which lasted to six months.

Degranol. Degranol, 1,6-bis(2-chloroethylamine)-1,6-deoxy-D-mannitol dihydrochloride, or mannomustine, or BCM caused remis-

sions in 16 of 21 Eckhardt (10) treated in a study comparing the results with those achieved with sarcolysin, TEM, HN2, etc. Scott (41) noted fair remissions in all five patients whom he observed on BCM for three to six months. Sandor *et al.* (40) recorded partial hematologic and clinical remissions in four of five patients, the longest improvement running to 15 months; they judged degranol to be less toxic than TEM. Barlow *et al.* (3) claimed only one good clinical and hematologic response in three cases of chronic lymphoid leukemia.

NH2. Host and Nissen-Meyer (18) described a moderate response in one patient following the use of HN2, or mustine. Eckhardt (10) observed no effect of this original N-mustard in one patient.

TS160. TS160, tris-2-chloroethylamine hydrochloride, or HN3, induced remissions in three of four patients treated by Libansky *et al.* (26).

CB1414. CB1414, 4-di-2'-chloroethylamine-2-methylazobenzene-2-carboxylic acid, produced three partial clinical and hematologic remissions in eight patients, according to Israels and Ritzmann (20).

Nitramin. Nitramin, methyl bis-(2-chloroethyl)amine-n-oxide, induced an objective remission for one month in one patient of Hammer and Tautenhahn (16).

Sarcolysin. Sarcolysin, chloroethylphenylalanine, when administered to three patients by Eckhardt (10) resulted in two remissions.

Amloclorin. Amloclorin, n,n-di-2-chloroethyl-gamma-p-aminophenylbutyric acid, administration to three patients resulted in fair amelioration in two in trials by Perrone *et al.* (34).

CB3025. CB3025, di-2-chloroethyl-p-aminophenylalanine, or the laevo isomer of sarcolysine, or melphalan, gave one good hematologic remission in four trials by Scott (41).

Embikhin. Embikhin, 2-chloroethyl-methylamine, was not as effective in the treatment of patients with chronic lymphoid leukemia as it was in chronic myeloid leukemia, according to Filimova *et al.* (11).

Combination Chemotherapy With N-Mustards. Aboul-Nasr (1) employed N-mustards in half a dozen combinations with other drugs in his control of patients with chronic lymphocytic leukemia: he noted two moderate remissions in two patients who received the combina-

tion HN2 plus cortisone plus ACTH; a 17 months' remission was induced in another patient by the combination HN2 plus nitramin plus cortisone plus ACTH; a moderate response of five months was noted after therapy with HN2 plus cortisone in another patient; nitramin plus cortisone gave a good remission lasting 22 months in yet another case; the combination nitramin plus cortisone plus TEM resulted in a good remission for 16 months; two patients receiving nitramin plus ultracortene enjoyed good remissions for eight and 35 months; and the combination nitramin plus cortisone plus HN2 resulted in a good remission for 44 months. Brenner (6) described a patient with chronic lymphoid leukemia who survived seven years but N-mustard therapy seemed to produce no effect on the course of the disease but, three years later, nose and gum bleeding responded to cortisone. Popescu *et al.* (35) reported a drop in leukocytes from 196,000 to 40,000 in one patient after administration of CB1348 and prednisone. Karaki (22) secured a brief clinical and hematologic response in one patient with the combination nitramin plus sarkomycin.

Chronic Granulocytic Leukemia

Chlorambucil. This nitrogen mustard leads also in the number of current studies which have been made on the management of chronic granulocytic leukemia. In a Cooperative Clinical Research Program of the Cancer Chemotherapy National Service Center (7), 12 of 21 patients had good to excellent responses to CB1348. Rundles *et al.* (37) reported similar results. Floksztrumpf and Isgro (12) induced a 15 months' remission in one patient with leukeran. Miller *et al.* (30) observed six marked objective remissions which averaged six weeks.

Dopan. In 1959, Shanbrom *et al.* (42) described the best responses in 14 chronic granulocytic and 11 chronic lymphocytic leukemias among all the hematologic diseases they treated. In 1960, they confirmed these results in two reports (43, 44) with 13 cases of chronic myelocytic leukemia. Blakhin (5) secured clinical improvement in three of four patients with this uracil mustard, and Lane *et al.* (24) noted one objective response in a patient with chronic granulocytic leukemia.

Degranol. Barlow *et al.* (3) observed five good and six fair clinical remissions lasting to 36 weeks, and eight good and two fair

responses hematologically in 12 patients; they concluded that mannomustine was not as effective as myleran or demecolcine in chronic granulocytic leukemia. Eckhardt (10) described responses in only three of nine patients with degranol, while eight of 11 had remissions on myleran therapy. Papac *et al.* (31, 32) in two studies recorded partial remissions in two patients who were administered mannitol mustard.

Embkhin. Filimova *et al.* (11) induced almost complete hematologic remissions and good clinical remissions lasting from two to 12 months in 10 patients given embikhin. Sherman *et al.* (45) secured some clinical improvement in three patients for two or three months, but they concluded the drug was too toxic.

Nitramin. Hammer and Tautenhahn (16) found that N-mustard oxide induced objective remissions in three patients who remained ambulatory at the time of reporting, six months after therapy. Kurokawa and Kaito (48) noted little effect of nitramin in five cases. Hiramitsu (17) described some remissions in patients with chronic myeloid leukemia, following nitramin therapy, and Kao *et al.* (21) described a patient who returned to work after treatment with this mustard.

Combination Chemotherapy With N-Mustards. Ginsburg (13) attempted to reduce refractoriness to irradiation by the use of sarcolysin, but he obtained no effect in children or adults with chronic granulocytic leukemia. Aboul-Nasr (1) described a good remission for seven months in a patient who was administered the combination nitramin plus TEM plus ultracortene. Miedzianowski (29) described a brief subjective and objective response in a patient on the combination N-mustard, vitamins, Fe, HCl, liver extract, antibiotics, and isonicotinic acid.

Discussion

A current study on the management of Hodgkin's disease and both acute and chronic forms of leukemia with the new N-mustard, Cytoxan or Endoxan (cyclophosphamide) (49), records 34 remissions in 55 patients (62 per cent remissions) with chronic lymphocytic leukemia, and 30 remissions in 37 patients (81 per cent remissions) with chronic granulocytic leukemia. In the present study, chlorambucil has been tested more extensively than Cytoxan but the results

with chronic lymphoid leukemia (141 remissions in 217 patients) are little better, while the results in chronic myeloid leukemia (19 remissions in 28 patients) are not as good as those with Cytoxan therapy. Dopan induced 33 responses in 58 patients and degranol 26 in 34 patients with chronic lymphoid leukemia. The trials with other new N-mustards on chronic leukemias are too few to warrant any conclusions, although some long remissions have been reported in combination chemotherapy with corticosteroids.

Acknowledgments

The original literature was made available by the National Library of Medicine and the libraries of Furman University and Greenville General Hospital.

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BOOK NOTICES*

Brief Course in Organic Chemistry. 2nd Edition. By Lyell C. Behr, Reynold C. Fuson, and Harold R. Snyder. 289 pp. John Wiley & Sons, Inc., New York, 1959. Price: $5.75.

This book provides short introductory chapters to orient the student in the language of organic chemistry and to introduce him to fundamental concepts with considerable clarity. The order of presentation of the previous edition of this book has been retained. The chapters have been expanded by the inclusion of additional material; emphasis is placed on the functional group.

A new feature of the book is the inclusion of questions at the ends of the chapters. They are designed to give the student practice in the application of the text material. There are additional illustrations of molecular models, examples of reactions, and explanations are presented in more detail. Those chapters dealing with ketones and aldehydes have been combined. Some of the titles of chapters have been altered in accordance with the revision of their contents. New chapters entitled "Homologues Series," "Naturally Occurring Esters," and "Sulfur Compounds" are included.

Progress in Medical Virology, Vol. 2. Edited by E. Berger and J. L. Melnick. 234 pp. Hafner Publishing Company, Inc., New York, N. Y., 1959. Price: $10.25.

Chemotherapeutic and prophylactic agents of virus infections are discussed on the experimental and biochemical basis. The mechanism of action of these different agents is explained with illustrations of structures of the compounds involved. Pictures of electron microscopy of viruses in thin sections of cells grown in cultures are given and explained. There are chapters on the metabolism of virus-infected animal cells, the salivary gland viruses of man and animals, viruses of respiratory tract, and the poliomyelitis-like properties of AB-IV-Coxsackie A 7 Group of Viruses. Bibliography and references are available for each chapter.

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* Through the cooperation of the library staff, Philadelphia College of Pharmacy and Science.

World Health Organization Technical Report Series No. 211. Expert Committee on Addiction-Producing Drugs, Eleventh Report. 16 pp. World Health Organization, Geneva, 1961. Also published in French and Spanish. Price: $0.30.

The World Health Organization Expert Committee on Addiction-Producing Drugs recommends that the following substances should be subject to the provisions of the 1931 Convention in respect of addiction-producing drugs comparable to morphine: clonitazine, diampromide, diphenoxylate, etonitazine, hydromorphinol, phenamphromide, and phenoperidine. The committee emphasizes the need for appropriate control measures on a national level to prevent the abuse of amphetamines and amphetamine-like substances contained in weight-reducing medicines and a strong need for improvement in regard to the information given on the possibilities of addiction liability of new drugs, particularly where analgesic and antitussive properties are concerned.

This report contains a list of drugs under International Narcotic Control.

Basic Pharmacology for Nurses. Second Edition, edited by Jessie E. Squire. 275 pp. The C. V. Mosby Company, St. Louis, Missouri, 1961. Price: $3.50.

This book has been written in a manner that simplifies the study of pharmacology for nurses. The theory and facts concerning medicine and drugs have been correlated step by step with practice in drug administration, and the entire text is organized to encourage the nurse in self-help study and testing.

The book is designed to help student nurses understand their responsibility in administering medication and to appreciate the necessary limitations imposed on nurses in this function. The text includes basic information concerning the main effects, uses, and doses of the common drugs, together with weights, measurements, abbreviations commonly used in medicine, directions for the use of tuberculin, insulin, and other syringes, and provision for practice in correct methods of administration of medicines.

Textbook of Biochemistry, 3rd Edition, by E. S. West and W. R. Todd. 1423 pp. Macmillan, New York, 1961. Price: $16.75.

This is the third edition in ten years of West and Todd's text and, again, the authors have tried to keep abreast of a rapidly moving field. The "abbreviated" list of publications in the field of biochemistry given at the close of the introduction has doubled since the 1952 edition, and most of the new additions are journals. The format of this edition is largely the same as the previous texts, but some of the chapters have been extensively revised. A new chapter dealing with the composition and metabolism of special tissues has been added. A separate chapter was created for a discussion of nucleic acid metabolism, due to the recent advances in this area. In order to preserve space, the authors have relegated some of the more detailed information into smaller print, and have made use of cross-references, rather than repeating some material.

Russian Drug Index, compiled by Stanley Jablonski. 103 pp. National Library of Medicine, U. S. Department of Health, Education, and Welfare. Public Health Service Publication #814, Public Health Service, Washington, D. C., 1961.

This index is an attempt to classify drugs used in Russia under the familiar drug names used in the West. The material in the text was taken from the principal pharmacological and medical works in monograph and serial form published in the Soviet Union from 1950 to 1960 which were available in the National Library of Medicine. The names of drugs developed in the Soviet Union as well as names of drugs developed elsewhere but renamed in the Soviet Union are included in the index. Special attention is given to the indigenous Soviet preparations such as biogenic stimulators, phytoncides, and extracts from Russian plants, little known outside the Soviet Union. Chemical preparations used in medical and paramedical technology are included. Each entry in the subject section, which is arranged alphabetically under broad function groups, includes the chemical formula or composition, a structural formula, a short description of drug properties, a Russian source, and an American bibliographic reference when available.

Listeriosis, by H. P. R. Seeliger. 308 pp. Hafner Publishing Co., New York, 1961. Price: $14.25.

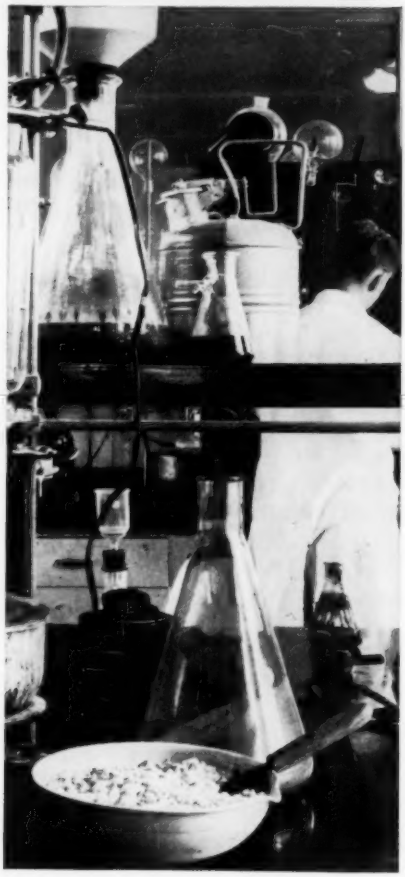
In 1955, Dr. H. P. R. Seeliger reviewed and analyzed the subject, listeriosis, in a monograph. A second edition, published in 1957, amplified the text. This is an English text of a new edition, brought up to date with charts, photographs, and a complete bibliography on this wide-spread disease. A detailed description of the clinical symptomatology and treatment of listeriosis is included for the physician. An up-to-date review of *Listeria monocytogenes,* its pathogenic activity, and its toxonomic position is presented to the laboratory worker. A detailed section on diagnostic procedures has been added.

Bulletin of the Medical Library Association. Vol. 49, No. 1 (Part 2 of 2 parts). The National Library of Medicine. **Index Mechanization Project, July 1, 1958-June 30, 1960.** Washington D. C., 1961. Price: $1.75.

This publication consists of a report on the fashioning of the new *Index Medicus* publication system. It begins with the history of large-scale indexing of current medical journal literature. The contents of the report embraces subjects such as: Preliminary, Composition, Punched Card Preparation, The New *Index Medicus* System, Operational History, Cost, General Appraisal, The Bibliographical Retrieval System, and Applications. The literature is supplemented by illustrations, charts, and graphs which gives a better understanding of the *Index Medicus* publication system.

Selective Toxicity. Second Edition. By Adrien Albert. 233 pp. John Wiley & Sons, Inc., New York, 1960. Price: $5.50.

This book is concerned with selectively toxic agents which injure some kinds of cells and not others, even when the two kinds are growing together. Hence, drugs, weed killers, and insecticides form the framework of this book. They are discussed from their physical, chemical, and structural aspects. The book is divided into two parts: part one being topics of general interest and part two, the relationship between structure and biological activity. An extensive bibliography is included.



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